Amendments to the Specification:

Please replace the title at page 1 with the following title:

~~Crystal Structure of BACE and Uses Thereof~~ Method for Identifying Agents that Interact with Beta-Site APP Cleaving Enzyme (BACE)

Please replace the paragraph **[0014]** beginning at page 4 with the following amended paragraph:

~~Figure 1 provides~~ Figures 1A-1EEE provide the atomic structural coordinates for BACE and the APP inhibitor peptide as derived by X-ray diffraction of a crystal of the BACE and APP inhibitor peptide complex. "Atom type" refers to the atom whose coordinates are being measured. "Residue" refers to the type of residue of which each measured atom is a part – *i.e.*, amino acid, cofactor, ligand or solvent. The "x, y and z" coordinates indicate the Cartesian coordinates of each measured atom's location in the unit cell (Å). "Occ" indicates the occupancy factor. "B" indicates the "B-value", which is a measure of how mobile the atom is in the atomic structure ($Å^2$).

Please replace the paragraph **[0016]** beginning at page 5 with the following amended paragraph:

Unless otherwise noted, "BACE" is Beta-site APP Cleaving Enzyme, and is the β-secretase enzyme that cleaves β-amyloid precursor protein (APP) at residue 671 (770aa isoform of APP numbering). After cleavage of APP by BACE, the remaining APP is cleaved at residue 716 by γ-secretase, leaving a 42 amino acid fragment of APP that is found in the proteinaceous plaques of Alzheimer's patients. The amino acid sequence of BACE preferably has the amino acid sequence deposited with Swiss Prot under accession number P56817 (SEQ ID NO:1), including conservative substitutions. As used herein, BACE also includes "BACE peptides," which are molecules having less than the complete amino acid sequence of BACE. Preferably,

BACE peptides include the active site in which BACE binds to and cleaves APP. Most preferably, the BACE peptide corresponds to amino acid residues 58-447 set forth in ~~Figure 1~~Figures 1A-1EEE ("$BACE_{58-447}$)", including conservative substitutions.

Please replace the paragraph **[0021]** beginning at page 6 with the following amended paragraph:

"Structural coordinates" are the Cartesian coordinates corresponding to an atom's spatial relationship to other atoms in a molecule or molecular complex. Structural coordinates may be obtained using x-ray crystallography techniques or NMR techniques, or may be derived using molecular replacement analysis or homology modeling. Various software programs allow for the graphical representation of a set of structural coordinates to obtain a three dimensional representation of a molecule or molecular complex. The structural coordinates of the present invention may be modified form the original set provided in ~~Figure 1~~Figures 1A-1EEE by mathematical manipulation, such as by inversion of integer additions or subtractions. As such, it is recognized that the structural coordinates of the present invention are relative, and are in no way specifically limited by the actual x, y, z coordinates of ~~Figure 1~~Figures 1A-1EEE.

Please replace the paragraph **[0024]** beginning at page 7 with the following amended paragraph:

The numbering of the amino acid residues identified in ~~Figure 1~~Figures 1A-1EEE are based on the numbering of the full length BACE protein from the start of the signal sequence. It will be obvious to the skilled practitioner that the numbering of the amino acid residues of BACE may be different than that set forth herein or may contain certain conservative amino acid substitutions that yield the same three dimensional structures as those defined in ~~Figure 1~~ Figures 1A-1EEE. Corresponding amino acids and conservative substitutions in other isoforms or analogues are easily identified by visual inspection of the relevant amino acid sequences or by

using commercially available homology software programs (*e.g.*, MODELLAR, MSI, San Diego, CA).

Please replace the paragraph **[0028]** beginning at page 8 with the following amended paragraph:

The present invention is directed to a crystallized complex of BACE and an APP inhibitor peptide that effectively diffracts X-rays for the determination of the structural coordinates of the complex. As used herein, BACE preferably corresponds to $BACE_{58-447}$ as set forth in ~~Figure 1~~Figures 1A-1EEE, with the N-terminal domain consisting of amino acid residues 58-207 shown in ~~Figure 1~~Figures 1A-1EEE, and the C-terminal domain consisting of amino acid residues 208-447 shown in ~~Figure 1~~Figures 1A-1EEE. The APP inhibitor peptide is preferably SER-GLU-VAL-ASN-Sta-VAL-ALA-GLU-PHE (SEQ ID NO:3).

Please replace the paragraph **[0030]** beginning at page 8 with the following amended paragraph:

Accordingly, the present invention also provides the three dimensional structure of BACE as derived by x-ray diffraction data of the BACE/APP inhibitor peptide crystal. Specifically, the three dimensional structure of BACE is defined by the structural coordinates shown in ~~Figure 1~~Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of the amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å. The structural coordinates of BACE are useful for a number of applications, including, but not limited to, the visualization, identification and characterization of various active sites of BACE, and the BACE/APP inhibitor peptide complex, including the APP or APP peptide binding site. The active site structures may then be used to design agents ~~with~~that interact with BACE, as well as BACE complexed with APP, an APP peptide or related molecules.

Please replace the paragraph **[0031]** beginning at page 9 with the following amended paragraph:

The present invention is also directed to an active site of an APP binding protein or peptide, preferably the APP peptide binding site of BACE, which comprises the relative structural coordinates according to ~~Figure 1~~Figures 1A-1EEE of residues SER71, GLY72, LEU91, ASP93, GLY95, SER96, VAL130, PRO131, TYR132, THR133, GLN134, ILE171, ILE179, ILE187, ALA188, ARG189, PRO190, TRP258, TYR259, ASP284, LYS285, ASP289, GLY291, THR292, THR293, ASN294, ARG296 and ARG368, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å.

Please replace the paragraph **[0032]** beginning at page 9 with the following amended paragraph:

In another preferred embodiment, the active site of an APP binding protein or peptide, preferably the APP peptide binding site of BACE, comprises the relative structural coordinates according to ~~Figure 1~~Figures 1A-1EEE of residues LYS70, SER71, GLY72, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE171, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, WER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396 and ILE447, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å.

Please replace the paragraph **[0033]** beginning at page 10 with the following amended paragraph:

Another aspect of the present invention is directed to a method for identifying an agent that interacts with an active site of BACE comprising the steps of: (a) determining an active site of BACE from a three dimensional model of BACE using the relative structural coordinates of ~~Figure 1~~Figures 1A-1EEE, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å; and (b) performing computer fitting analysis to identify an agent which interacts with said active site. Computer fitting analyses utilize various computer software programs that evaluate the "fit" between the putative active site and the identified agent, by (a) generating a three dimensional model of the putative active site of a molecule or molecular complex using homology modeling or the atomic structural coordinates of the active site, and (b) determining the degree of association between the putative active site and the identified agent. Three dimensional models of the putative active site may be generated using any one of a number of methods known in the art, and include, but are not limited to, homology modeling as well as computer analysis of raw data generated using crystallographic or spectroscopy data. Computer programs used to generate such three dimensional models and/or perform the necessary fitting analyses include, but are not limited to: GRID (Oxford University, Oxford, UK), MCSS (Molecular Simulations, San Diego, CA), AUTODOCK (Scripps Research Institute, La Jolla, CA), DOCK (University of California, San Francisco, CA), Flo99 (Thistlesoft, Morris Township, NJ), Ludi (Molecular Simulations, San Diego, CA), QUANTA (Molecular Simulations, San Diego, CA), SYBYL (TRIPOS, Inc., St. Louis, MO) and LEAPFROG (TRIPOS, Inc., St. Louis, MO).

Please replace the paragraph **[0034]** beginning at page 10 with the following amended paragraph:

The present invention also provides a method for identifying an agent that interacts with an active site of an APP binding protein or peptide, and preferably the APP peptide binding site on BACE. The method comprises the steps of: (a) generating a three dimensional model of an active site of an APP binding protein or peptide using the relative structural coordinates according to ~~Figure 1~~Figures 1A-1EEE of residues SER71, GLY72, LEU91, ASP93, SER96, VAL130, PRO131, TYR132, THR133, GLN134, ILE171, ILE179, ILE187, ALA188, ARG189, PRO190, TRP258, TYR259, ASP284, LYS285, ASP289, GLY291, THR292, THR293, ASN294, ARG296 and ARG368, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å; and (b) designing an agent using the three dimensional model generated in step (a). In another preferred embodiment, the active site of the APP binding protein or peptide is generated using the three dimensional model defined by the relative structural coordinates according to ~~Figure 1~~Figures 1A-1EEE of residues LYS70, SER71, GLY72, GLN73, GLY74, TYR75, LEU91, VAL92, ASP93, THR94, GLY95, SER96, SER97, ASN98, TYR129, VAL130, PRO131, TYR132, THR133, GLN134, GLY135, LYS136, TRP137, LYS168, PHE169, PHE170, ILE171, ASN172, SER174, TRP176, GLY178, ILE179, LEU180, GLY181, ALA183, TYR184, ALA185, GLU186, ILE187, ALA188, ARG189, PRO190, ASP191, ASP192, ARG256, TRP258, TYR259, TYR283, ASP284, LYS285, SER286, ILE287, VAL288, ASP289, SER290, GLY291, THR292, THR293, ASN294, LEU295, ARG296, GLY325, GLU326, ARG368, VAL370, LYS382, PHE383, ALA384, ILE385, SER386, GLN387, SER388, SER389, THR390, GLY391, THR392, VAL393, GLY395, ALA396 and ILE447, ± a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, preferably not more than 1.0Å, and most preferably not more than 0.5Å.